# Geographical prevalence and factors associated with multidrug-resistant tuberculosis

Xiaoan Wang, Xueying Fan, Mawurupa Xiaohelaiti, Dongdong Su*

The Sixth People's Hospital of Xinjiang Uygur Autonomous Region, China

**Submitted:** 27 April 2026; **Accepted:** 20 August 2026
**Online publication:** 26 November 2026

Arch Med Sci
DOI: https://doi.org/10.5114/aoms/231345
Copyright © 2026 Termedia & Banach

***Corresponding author:**
Dongdong Su
The Sixth People's Hospital of Xinjiang Uygur Autonomous Region, China
E-mail: sdd460308826@sina.com

## Abstract

**Introduction:** The rise of drug-resistant tuberculosis (DR-TB), particularly multidrug-resistant (MDR-TB), has become a significant public health concern globally, particularly in developing countries.
**Material and methods:** The geographical distribution and corresponding risk factors associated with MDR-TB were investigated using a multilevel analysis. A total of 249,344 patients from 123 studies were included.
**Results:** In Asia, Africa, Europe, and South America, the corresponding rates of MDR-TB among patients with TB were 8.6%, 3.9%, 4.2%, and 14.8%. The odds of MDR-TB were higher in patients with HIV (OR = 2.68, 95% CI: 2.40–2.98), older age (> 50 years, 77%), alcohol users (OR = 47.87, 95% CI: 43.31–52.91), and those living in rural areas (OR = 17.0, 95% CI: 15.73–18.43), according to the odds ratio analysis. According to the polynomial regression analysis, urban residence was a reliable indicator of MDR-TB. Using network analysis, we identified the factors most associated with MDR-TB differentially across all regions (nonlinearly: residence in Europe; linearly: smoking), Asia (both linearly and nonlinearly: smoking), Africa (linearly: smoking; nonlinearly: male sex), Europe (linearly: HIV; nonlinearly: alcohol use), and South America (nonlinearly: HIV).
**Conclusions:** The prevalence of MDR-TB and associated risk factors varies by geographical location. When making decisions to enhance medical practice in managing MDR-TB at the regional level, this variation should be considered.

**Key words:** geographical prevalence, risk factors, multidrug-resistant tuberculosis, network analysis.

## Introduction

Among the top 10 causes of mortality worldwide, tuberculosis (TB) is more prevalent than human immunodeficiency virus (HIV) [1]. The bacterium that causes this illness is known as *Mycobacterium tuberculosis* [2]. Although the lungs are typically affected, other organs, such as the kidneys and brain, can also be affected by TB [3]. According to the World Health Organization (WHO), there were approximately 10.6 million cases of TB worldwide in 2021 (134 cases per 100,000 people) [4]. Globally, TB claimed 1.3 million lives in 2022, down from an expected 1.4 million in 2020 and 2021 [5]. With 167,000 fatalities in 2022, TB was the primary cause of death among patients with HIV. In 2022, almost 7.5 million people received a TB diagnosis; 46% of these individuals reside in Southeast Asia, 23% in Africa, and 18% in the Western Pacific [5]. Approximately



Creative Commons licenses: This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY -NC -SA 4.0). License (http://creativecommons.org/licenses/by-nc-sa/4.0/).

10.6 million individuals worldwide now have active TB, with 5.8 million being male, 3.5 million being female, and 1.3 million being children [5]. Furthermore, 5–10% of the world's population develops active TB, accounting for approximately 25% of all infections [5]. Pre-extensively drug-resistant (pre-XDR), MDR, and extensively drug-resistant (XDR) are the three different types of TB [3]. The WHO classifies DR-TB as follows: isoniazid (also known as isonicotinic acid hydrazide, INH)-resistant, rifampicin (Rif)-resistant, pre-XDR (resistance to any fluoroquinolone), XDR (additional resistance to at least one fluoroquinolone and at least one second-line injectable medication), MDR (resistance to both Rif and INH), and INH-resistant [6].

MDR-TB is a global issue. Instances of MDR-TB incidents increased 3.1% from 437,000 in 2020 to an expected 450,000 in 2021 [6]. Approximately 500,000 persons worldwide are believed to have contracted Rif-TB, with 78% of those cases being MDR-TB [7]. MDR-TB requires more costly and potentially more toxic medications than those used for drug-susceptible TB, such as INH and Rif [8]. An estimated 600000 new cases of DR-TB were reported worldwide in 2016. Eighty-two percent (490000) of these patients had MDR-TB [8]. Rif resistance is mostly caused by mutations in the rifampicin resistance-determining region (RRDR) of *rpoB*, with codons 450, 445, and 435 being the most common places [9]. Mutations in *katG* are the primary cause of INH resistance, followed by those in the *oxyR-ahpC* intergenic region and the *inhA* promoter [10]. Mutations in *rpoB* and *katG* were responsible for 65–88.5% of INH resistance [11, 12] and 91.1%–97.7% of Rif resistance, respectively [13, 14]. The most potent anti-TB medications and the cornerstone of first-line anti-TB therapy are INH and Rif. Resistance to Rif and INH forces the use of less effective, more costly, and potentially more toxic second-line anti-TB medications [15]. Anti-TB drug resistance is closely linked to challenges in TB control [16]. As a result, it has impacted control initiatives in nations where second-line anti-TB medications are not easily accessible [17]. One of the biggest challenges to global TB disease control is the emergence and spread of Rif- or MDR-TB [18]. Thus, understanding the factors that influence TB control programs and are linked to MDR is essential.

Significantly more common co-existing factors in patients with MDR-TB include comorbidities (such as diabetes mellitus and HIV), sociodemographic traits (such as gender, age, location of residence, education, and marital status), and unhealthy behaviors like smoking and alcohol consumption [19]. Although there have been many studies on individual risk factors for MDR-TB, there is limited literature that provides a comprehensive assessment of the epidemiological situation of MDR-TB worldwide. Because of the inconsistent reporting of many epidemiological variables in the reviewed literature, this study concentrated on the most frequently reported risk factors for the purpose of quantitative synthesis, while recognizing that other factors may also contribute to the emergence of MDR-TB. Therefore, the purpose of this multi-step analysis was to combine the published findings of previous research to identify the elements most linked to MDR. These multilevel and network analysis techniques allow us to assess the potential region-specificity of the risk factors and the geographical burden of MDR-TB.

The results of our study may help health policymakers to better consider the most important factors influencing the prevalence of MDR.

## Material and methods

### Study selection

The PubMed, Google Scholar, Science Direct, Embase, Scopus, and Web of Science databases were searched using the following keywords: prevalence, drug-resistant tuberculosis, multidrug-resistant tuberculosis, burden, outbreak, and their combinations, using the AND and OR operators. There was no time restriction on the search, and it continued until August 2025. To ensure the thoroughness of the literature search, the reference lists of the recognized studies were also screened. The final analysis was limited to studies that met the inclusion criteria and reported the prevalence of MDR-TB by continent.

### Inclusion and exclusion criteria

Studies that reported the prevalence of MDR-TB (including cross-sectional, case-control, and cohort studies) were identified using the following criteria: studies that are available in full text, studies that were authored and published in English, and studies that included sufficient data (prevalence and sample size). In contrast, animal studies, reviews, meta-analyses, case reports, and case series studies were excluded (Supplementary Figure S1).

### Data extraction

Two researchers used separate checklists to accomplish data extraction. The initial author names, the year the study was published, the study location, the sample size, the age of the men and women, the prevalence of DR-TB and MDR-TB, and the research tools were all included in this checklist.

### Statistical analysis

The data distribution was not normal, as confirmed by the Anderson-Darling test. We used multivariate analytic methods in this study, including network analysis. The proposed method was used to better understand differences in MDR-TB prevalence by identifying and assessing patterns in the complex relationships between MDR-TB prevalence and other characteristics (e.g., age, sex, residence, and associated disorders such as HIV). This technique builds a network depending on how frequently nodes are connected [20, 21]. The network analysis was conducted using both Pearson linear and Spearman nonlinear similarity indicees along with the Fruchterman-Reingold method as a force-directed layout approach. Additionally, we estimated the relationships between MDR-TB prevalence and other variables using polynomial regression analysis (PRA). The PRA advanced one order at a time, from a first-order (linear) polynomial to a fifth-order polynomial. The most significant nth-order polynomial was identified. Network visualization analysis and PRA were performed using the PAST tool (http://folk.uio.no/ohammer/past). For the factors linked to MDR-TB, odds ratios (OR) and 95% confidence intervals (CI) were calculated. The significance level was set at $p < 0.05$.

## Results

Supplementary information shows the flow diagram of study selection. A total of 5298 articles were found in the databases after the first search. Because they appeared more than once in different databases, 2511 articles were eliminated. The titles and abstracts of the studies were examined during the screening phase, and 2664 additional papers were disqualified in accordance with the inclusion and exclusion criteria. Finally, 123 articles were selected for this study. The list (Supplementary Information) and the demographic and clinical characteristics of 123 studies with 249,344 patients with TB are presented in Supplementary Table SI. As shown in Table I, the mean age was 34.2 years (range: 2.1–80.3 years). There were 159,829 (64.1%) men among the patients, 1093 (0.44%) alcohol users, 2142 (0.86%) smokers, and 22875 (9.2%) HIV-positive patients. The largest proportion of men was in Europe (75.0%), followed by South America (67.5%), Asia (63.8%), and Africa (59.9%). The study included 24,642 (9.9%) patients from rural areas and 223,977 (89.8%) patients from urban areas. A total of 6917 (2.8%) children under the age of 18, 194,883 (78.2%) adults aged 18–50 years, and 14,095 (5.7%) older patients were included in the sample. Among patients with TB, Africa had the lowest mean age at 27.6 years, followed by Asia at

**Table I.** Sociodemographic and clinical characteristics of pulmonary tuberculosis (TB)

| TB patients | Age mean ± SD | Male *n* (%) | Alcohol *n* (%) | Rural *n* (%) | Urban No. (%) | Children *n* (%) | Adults *n* (%) | Elderly *n* (%) | HIV *n* (%) | Smoking *n* (%) | DR-TB *n* (%) | MDR-TB *n* (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Total *n* = 249344 | 34.2 ±13.2 | 159829 (64.1%) | 1093 (0.44%) | 24642 (9.9%) | 223977 (89.8%) | 6917 (2.8%) | 194883 (78.2%) | 14095 (5.7%) | 22875 (9.2%) | 2142 (0.86%) | 23238 (9.3%) | 14151 (5.7%) |
| Asia *n* = 67907 | 37.3 ±11.4 | 43325 (63.8%) | 185 (0.27%) | 3472 (5.1%) | 64215 (94.6%) | 2312 (3.4%) | 40932 (60.3%) | 5512 (8.1%) | 2450 (3.6%) | 1174 (1.7%) | 11650 (17.2%) | 5841 (8.6%) |
| Africa *n* = 140531 | 27.6 ±12.8 | 84178 (59.9%) | 393 (0.28%) | 21170 (15.1%) | 118567 (84.4%) | 2816 (2.0%) | 129176 (91.9%) | 2113 (1.5%) | 18923 (13.5%) | 440 (0.3%) | 4051 (2.9%) | 5538 (3.9%) |
| Europe *n* = 30699 | 39.0 ±7.2 | 23025 (75.0%) | 43 (0.14%) | 0 | 30699 (100%) | 582 (1.9%) | 20220 (65.9%) | 6261 (20.4%) | 230 (0.75%) | 60 (0.2%) | 3098 (10.1%) | 1285 (4.2%) |
| South America *n* = 9537 | 40.0 ±17.8 | 6437 (67.5%) | 515 (5.4%) | 0 | 9537 (100%) | 1292 (13.5%) | 4746 (49.8%) | 224 (2.3%) | 1271 (13.3%) | 504 (5.3%) | 4048 (42.4%) | 1414 (14.8%) |

*TB – tuberculosis, DR – drug-resistant, MDR – multidrug-resistant.*

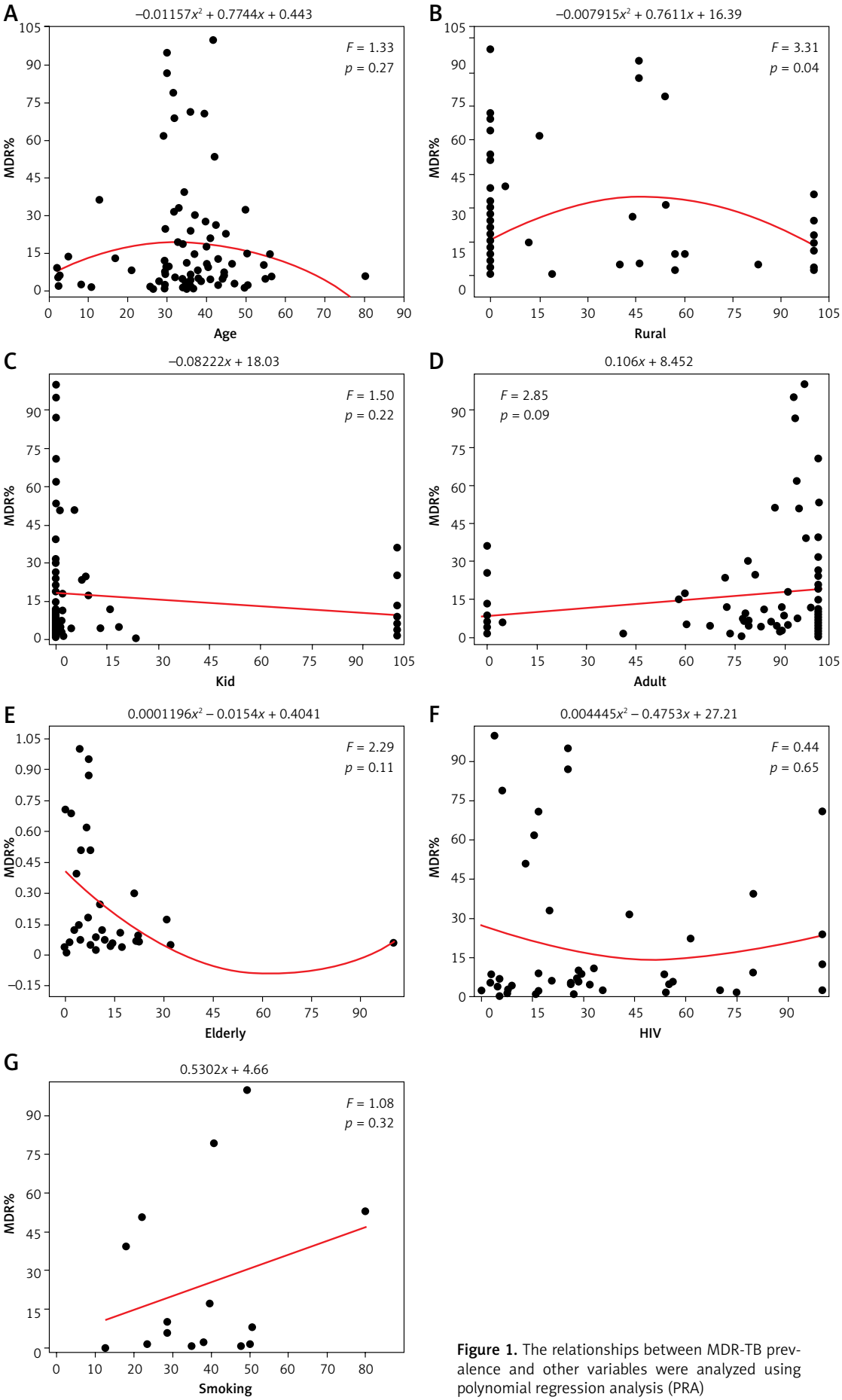



**Figure 1.** The relationships between MDR-TB prevalence and other variables were analyzed using polynomial regression analysis (PRA)

37.3 years, Europe at 39.0 years, and South America at 40.0 years (Table I).

Among patients with TB, South America had the largest proportion of children (< 18 years) at 13.5%, followed by Asia (3.4%), Africa (2.0%), and Europe (1.9%). Africa (91.9%) had the highest percentage of adults (18–60 years), followed by Europe (65.9%), Asia (60.3%), and South America (49.8%). Among patients with TB, Europe had the highest proportion of older patients (20.4%), followed by Asia (8.1%), South America (2.3%), and Africa (1.5%) (Table I).

As shown in Table I, Africa had the largest percentage of patients with TB among rural regions (15.1%), followed by Asia (5.1%). In Europe and South America, the highest proportion of patients was from urban regions (100%). Among patients with TB, South America accounted for the highest percentage of alcoholics (5.4%), followed by Africa (0.28%), Asia (0.27%), and Europe (0.14%). Africa had the highest rate of HIV infection among patients with TB (13.5%), followed by South America (13.3%), Asia (3.6%), and Europe (0.75%). South America had the highest smoking prevalence among patients with TB (5.3%), followed by Asia (1.7%), Africa (0.3%), and Europe (0.2%).

### Overall prevalence of any first-line drug-resistant and multidrug-resistant TB

The prevalence rates of drug-resistant TB (DR-TB) and multidrug-resistant TB (MDR-TB) were 9.3% and 5.7%, respectively (Table I). South America (42.4%) had the greatest prevalence of DR-TB, followed by Asia (17.2%), Europe (10.1%), and Africa (2.9%). South America (14.8%) had the highest prevalence of MDR-TB, followed by Asia (8.6%), Europe (4.2%), and Africa (3.9%) (Table I).

### Polynomial regression analysis to identify the best predictor of MDR-TB

Rural residence was quadratically associated with MDR-TB ($F$ = 3.31, $p$ = 0.04) using polynomial regression analysis (Figure 1). MDR-TB was linearly associated with adulthood ($F$ = 2.85, $p$ = 0.09; Figure 1).

### Odd ratios to determine factors associated with MDR-TB

Table II lists the factors linked to MDR-TB. We found that MDR-TB risk was significantly higher in alcoholic patients vs. non-alcoholic patients (OR = 47.87, 95% CI: 43.31–52.91; $p$ < 0.0001), HIV-positive patients vs. HIV-negative patients (OR = 2.68, 95% CI: 2.40–2.98; $p$ < 0.0001), urban patients vs. rural patients (OR = 17.03, 95% CI: 15.73–18.43; $p$ < 0.0001), older patients (> 60 years) vs. children (OR = 1.77, 95% CI: 1.51–2.07; $p$ < 0.0001), and older patients vs. adults (OR = 1.85, 95% CI: 1.65–2.08; $p$ < 0.0001). The prevalence of MDR-TB was not different between adults (18–50 years) and children (< 18 years) (OR = 0.95, 95% CI: 0.85–1.07; $p$ = 0.212; Table II).

### Network analysis: MDR-TB in the entire sample

Network analysis revealed that the factors most closely associated with the prevalence

**Table II.** Factors associated with multidrug-resistant tuberculosis (MDR-TB)

| Factor | No. of susceptible patients with TB | No. of patients with MDR-TB | MDR TB vs. susceptible TB | |
|---|---|---|---|---|
| | | | Odds ratio (95% CI) | *P* value |
| Age | | | | |
| Children | 4407 | 340 | Ref. | |
| Adults | 91133 | 6714 | 0.95 (0.85–1.07) | 0.212 |
| Older adults | 2540 | 347 | 1.77 (1.51–2.07) | 0.0001 |
| Adults | | | Ref. | |
| Older adults | | | 1.85 (1.65–2.08) | 0.0001 |
| Alcohol use | | | | |
| Non-alcoholic | 211903 | 12625 | Ref. | 0.0001 |
| Alcoholic | 535 | 1526 | 47.87 (43.31–52.91) | |
| Residence area | | | | |
| Rural | 19165 | 697 | Ref. | 0.0001 |
| Urban | 19115 | 11836 | 17.03 (15.73–18.43) | |
| HIV | | | | |
| Negative | 179287 | 10093 | Ref. | 0.0001 |
| Positive | 2583 | 389 | 2.68 (2.40–2.98) | |

*P < 0.05 (significant), CI – confidence interval, TB – tuberculosis, MDR – multidrug-resistant.*

of MDR-TB were smoking (linearly; Figure 2 A) and Europe (nonlinearly; Figure 2 B). The factors most associated with the prevalence of DR-TB were rural residence (both linearly and nonlinearly; Figures 2 A, B). The factors most associated with the prevalence of MDR-TB in men (mMDR-TB) were smoking (linearly; Figure 2 A) and adulthood (nonlinearly; Figure 2 B). Alcohol use (linearly; Figure 2 A) and older age (nonlinearly; Figure 2 B) were the factors most associated with the prevalence of MDR-TB in women (fMDR-TB).

### Network analysis: MDR-TB in Asia

According to the network analysis (both linearly and nonlinearly), in Asia, smoking and rural residence were the factors most related to MDR-TB and DR-TB, respectively (Figures 3 A, B). The factors most associated with the prevalence of mMDR-TB were smoking (linearly, Figure 3 A) and adulthood (Spearman correlation; Figure 3 B). Rural residence was the most common factor associated (nonlinearly) with fMDR-TB in Asia (Figure 3 B).

### Network analysis: MDR-TB in African populations

In Africa, the factors most associated with MDR-TB were smoking (linearly; Figure 4 A) and male sex (nonlinearly; Figure 4 B). Rural residence was the factor most associated with DR-TB risk in Africa (both linearly and nonlinearly; Figures 4 A, B). Network analysis revealed that smoking (linearly; Figure 4 A) and adulthood (nonlinearly; Figure 4 B) were the factors most associated with mMDR-TB in African populations. We found that alcohol use (linearly; Figure 4 A) and older age (nonlinearly; Figure 4 B) were the factors most associated with fMDR-TB in Africa.

### Network analysis: MDR-TB in Europe

Network analysis identified HIV (linearly; Figure 5 A) and alcohol use (nonlinearly; Figure 5 B) as the factors most associated with MDR-TB. We found that adulthood (linearly; Figure 5 A) and alcohol use (nonlinearly; Figure 5 B) were the factors most associated with DR-TB. The network showed that HIV (linearly; Figure 5 A) and male

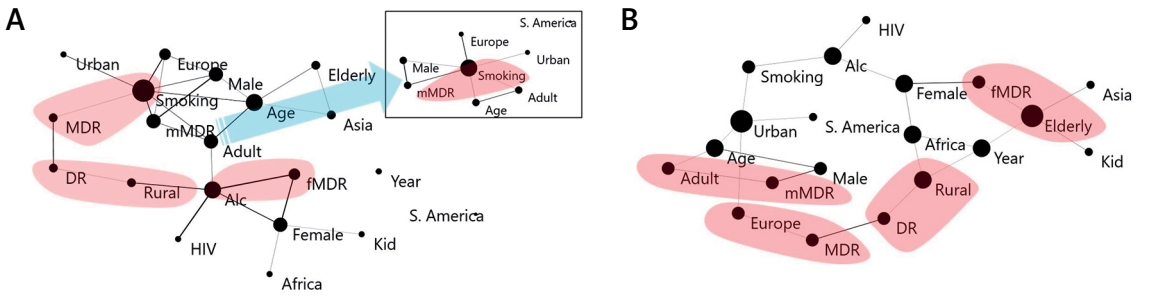



**Figure 2.** The complex relationships between drug-resistant tuberculosis and risk factors in the entire sample (all regions). Network analysis was conducted based on (**A**) Pearson correlation index at the highest cutoff value of 69% (rectangular panel: cutoff point at 67%) and (**B**) Spearman correlation index at the highest cutoff value of 58%. Clustering and correlation coefficients are represented by the size of the nodes (variables) and edges (interactions between parameters). Small nodes and thin edges denote low values

*MDR – multidrug-resistant tuberculosis, DR – any first-line drug resistance, Alc – alcohol use, mMDR – MDR risk in men, fMDR – MR risk in women, S – south, HIV – human immunodeficiency virus.*

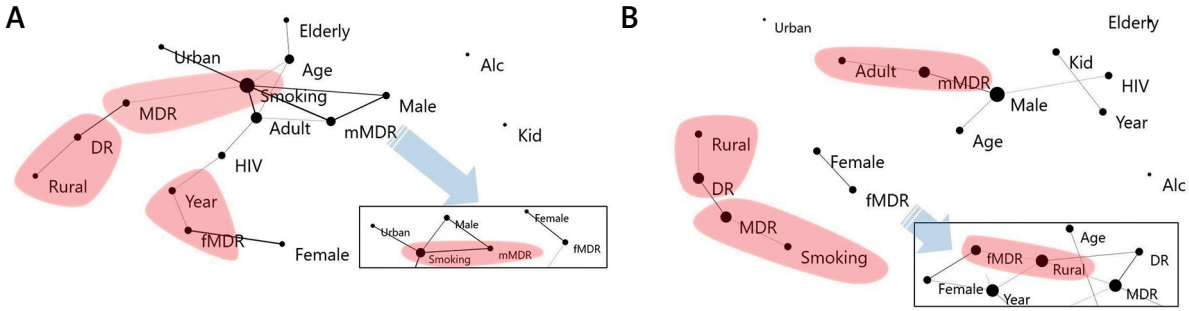



**Figure 3.** The intricate relationships between drug-resistant tuberculosis and risk factors in Asia. Network analysis based on (**A**) Pearson correlation index at the highest cutoff value of 65% (right rectangular panel: cutoff point at 67%) and (**B**) Spearman correlation index at the highest cutoff value of 60% (rectangular panel: cutoff point at 58%). Clustering and correlation coefficients are represented by the size of the nodes (variables) and edges (interactions between parameters). Small nodes and thin edges denote low values

*MDR – multidrug-resistant tuberculosis, DR – any first-line drug resistance, Alc – alcohol use, mMDR – MDR risk in men, fMDR – MR risk in women, S – south, HIV – human immunodeficiency virus.*

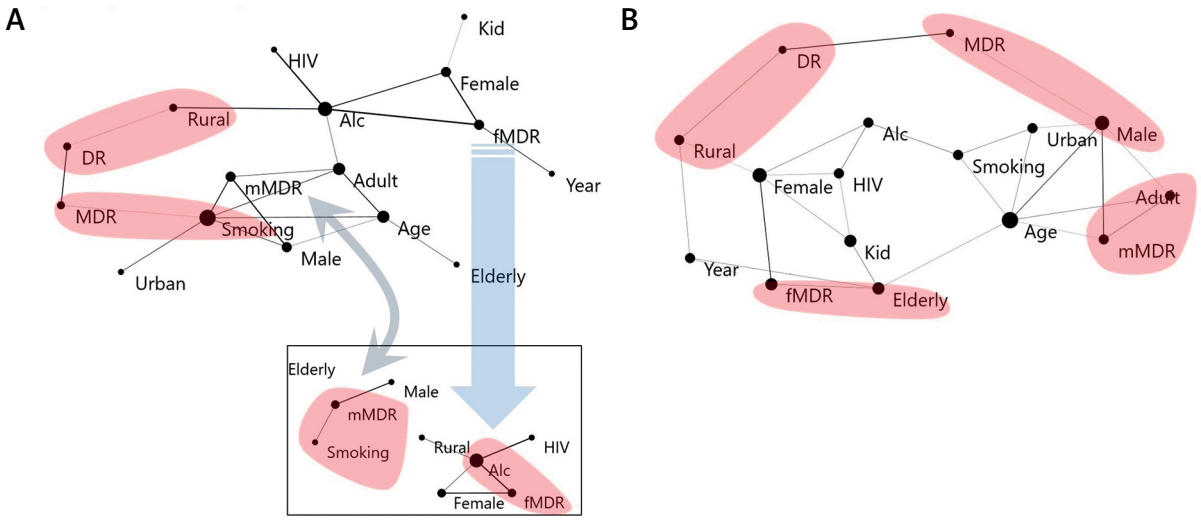



**Figure 4.** The intricate relationships between drug-resistant tuberculosis and risk factors in Africa. Network analysis based on (**A**) Pearson correlation index at the highest cutoff value of 60% (rectangular panel: cutoff point at 75%) and (**B**) Spearman correlation index at the highest cutoff value of 55%. Clustering and correlation coefficients are represented by the size of the nodes (variables) and edges (interactions between parameters). Small nodes and thin edges denote low values

*MDR – multidrug-resistant tuberculosis, DR – any first-line drug resistance, Alc – alcohol use, mMDR – MDR risk in men, fMDR – MR risk in women, S – south, HIV – human immunodeficiency virus.*

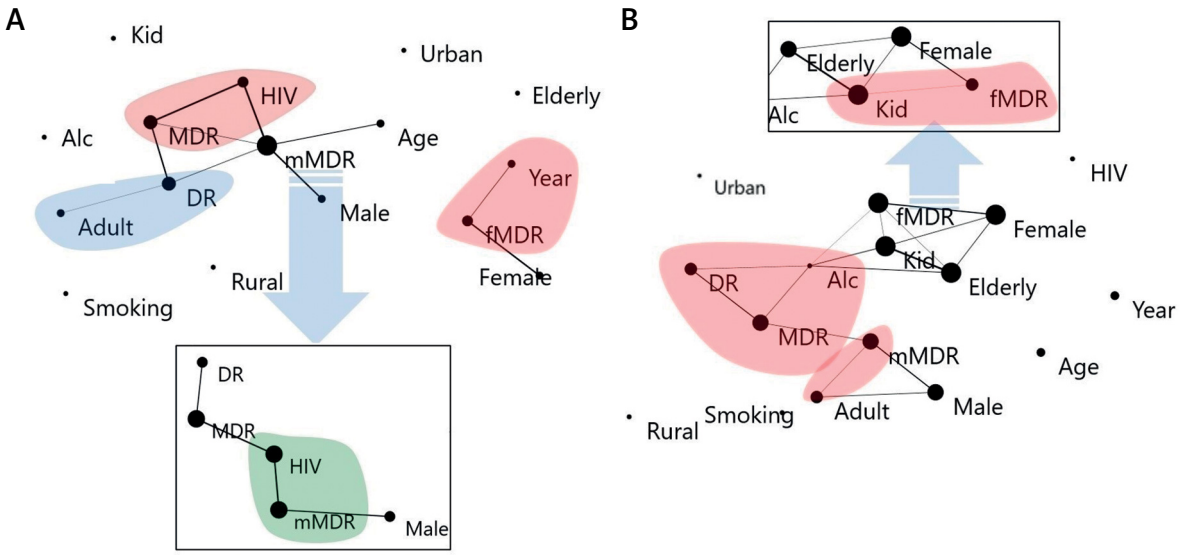



**Figure 5.** The intricate relationships between drug-resistant tuberculosis and risk factors in Europe. Network analysis was performed based on (**A**) Pearson correlation index at the highest cutoff value of 80% (rectangular panel: cutoff point at 89%) and (**B**) Spearman correlation index at the highest cutoff value of 77% (rectangular panel: cutoff point at 78.5%). Clustering and correlation coefficients are represented by the size of the nodes (variables) and edges (interactions between parameters). Small nodes and thin edges denote low values

*MDR – multidrug-resistant tuberculosis, DR – any first-line drug resistance, Alc – alcohol use, mMDR – MDR risk in men, fMDR – MR risk in women, S – south, HIV – human immunodeficiency virus.*

sex (nonlinearly; Figure 5 B) were the factors associated with mMDR-TB. The risk of fMDR-TB was associated with older age (linearly; Figure 5 A) and childhood (nonlinearly; Figure 5 B).

### Network analysis: MDR-TB in South America

In South America, MDR-TB risk was strongly associated with older age (linearly; Figure 6 A) and HIV (nonlinearly; Figure 6 B). We found that adulthood (linearly; Figure 6 A) and elderly age and male sex (nonlinearly; Figure 6 B) were the factors most associated with DR-TB in South America.

## Discussion

This investigation identified geographical variation in the prevalence of MDR-TB and related risk factors. The findings indicate that a multi-step

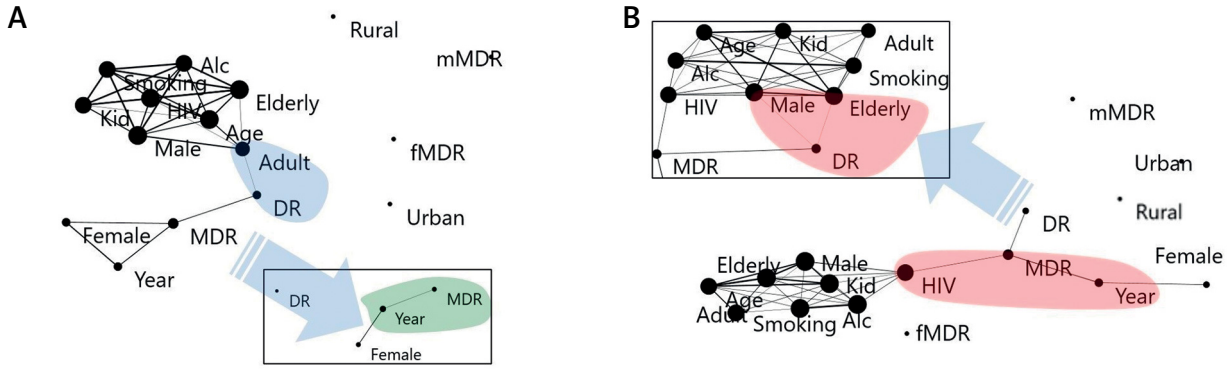



**Figure 6.** The intricate relationships between drug-resistant tuberculosis and risk factors in South America. Network analysis was conducted based on (**A**) Pearson correlation index at the highest cutoff value of 65% (rectangular panel: cutoff point at 79%) and (**B**) Spearman correlation index at the highest cutoff value of 60% (rectangular panel: cutoff point at 56.5%). Clustering and correlation coefficients are represented by the size of the nodes (variables) and edges (interactions between parameters). Small nodes and thin edges denote low values

*MDR – multidrug-resistant tuberculosis, DR – any first-line drug resistance, Alc – alcohol use, mMDR – MDR risk in men, fMDR – MR risk in women, S – south, HIV – human immunodeficiency virus.*

analysis, particularly network analysis, can be employed to better understand the intricate connections between MDR-TB and regionally specific risk variables.

This study aimed to use multilevel, polynomial, and network analyses to analyze the burden of and factors associated with MDR-TB; however, traditional systematic reviews are generally limited to estimating pooled prevalence or evaluating risk factors independently [22–26], reporting a local prevalence [22, 25] or global prevalence of MDR-TB [23, 26]. A limited number of parameters related to MDR-TB have been reported. Salari *et al.* (2023) [26], and Mughal *et al.* (2025) [23] investigated the global prevalence of MDR-TB with a limited number of parameters related to MDR-TB, including diabetes, smoking, age, and gender. The current study design enables the detection of linear and nonlinear patterns of relationships between epidemiological variables at many levels. This approach may help deepen our understanding of the complex relationships that drive regional heterogeneity of MDR-TB and may lead to more effective prevention and control strategies.

We found that the prevalence of MDR-TB (especially among men, mMDR-T) and DR-TB in all regions (in general), Asia, and Africa was strongly associated with smoking and rural residence. It is believed that smoking contributes to more than 20% of TB among adults, compared with 16% for HIV and 15% for diabetes [27]. In recent years, it has been shown that smoking is an independent risk factor for MDR-TB [28]. Tobacco smoking has been linked to an increased risk of TB infection, higher TB-related mortality, and poor treatment compliance [29, 30]. There are several explanations for the association between smoking and drug-resistant TB. Tobacco smoking may impair immune responses within the human body, contributing to the susceptibility to infection with some drug-resistant TB strains, such as MDR1 (INH + RIF). Furthermore, TB patients who use tobacco may have reduced adherence and be less likely to complete anti-TB medication, resulting in acquired resistance [31]. Recent studies have continued to strengthen the association between tobacco exposure and adverse TB outcomes. A recent systematic review demonstrated that tobacco use significantly increases the risk of poor treatment outcomes, recurrence, and mortality among patients with TB [32]. Similarly, a nationwide population-based cohort study reported that smoking substantially increased the risk of developing TB, reinforcing the biological plausibility that tobacco-induced impairment of pulmonary immune defenses may facilitate persistent infection and treatment failure [33]. These findings are consistent with our network analysis, which identified smoking as one of the factors most strongly associated with MDR-TB in several geographic regions. In conclusion, given the relationship between smoking and MDR-TB, the prevalence of MDR-TB and smoking, particularly in Asia and Africa, should be monitored, and awareness about the negative effects of tobacco use should be increased.

As mentioned above, network analysis revealed that rural residence was the factor most strongly associated with fMDR-TB and DR-TB risk in all regions, Asia, and Africa. TB has been reported to be more prevalent in rural regions than in cities [16]. We found that compared urban areas, the odds of MDR-TB were approximately 17-fold higher in rural areas. The reason could be that rural patients seek health care from traditional therapists, resulting in a delay in TB diagnosis and continuing disease transmission. Moreover, the high frequency of drug resistance in rural areas can be attribut-

ed to improper anti-TB medication delivery, easily accessible second-line drugs, and a comparatively weak case management system for patient follow-up throughout treatment [34]. The findings indicate that more targeted MDR-TB health programs should be considered in rural areas of Asia (especially among women) and Africa. Moreover, the observed variability in the distribution suggests that control measures need to be adapted to different epidemiological settings. Modifiable factors, such as smoking, HIV detection and treatment, alcohol use, and health service accessibility in rural areas, should be considered in the development of region-specific intervention strategies to reduce the impact of drug-resistant TB. Future studies that employ a similar design but were conducted at different centers should report their findings in a uniform manner to allow an appropriate assessment of risk factors [35, 36]. Further multicenter investigations addressing the epidemiology and management of MDR-TB are needed and should focus on patient groups in which multiple risk factors may interact to produce diverse clinical presentations.

In contrast to Asia and Africa, network analysis revealed that in Europe and South America, the MDR-TB and DR-TB risk followed a different pattern and were linearly associated with HIV infection (especially in men) and alcohol use. Furthermore, compared with HIV-negative individuals, the odds of MDR-TB were approximately 2.7-fold higher among HIV-positive individuals. Evidence regarding HIV infection as a risk factor for the occurrence or progression of MDR-TB is inconclusive. According to a Bayesian modeling study, HIV co-infection had no discernible impact on the transmissibility or mutation rate of TB and was not associated with a greater increase in resistance [37, 38]. Nevertheless, individuals living with HIV are more likely to develop DR-TB [39]. Rif-resistant-TB (4.9% vs. 3.2%) and MDR-TB (3.1% vs. 2.0%) are more common in HIV-positive than HIV-negative patients [40, 41]. In the United States and Europe, there have been significant outbreaks of MDR-TB in HIV-positive individuals, and there have been growing reports of drug-resistant strains of *Mycobacterium tuberculosis* among these patients [38, 42]. It appears that a relationship exists between HIV and MDR-TB. Univariate analysis revealed that the presence of MDR-TB was associated with a lower median CD4 count [43], with HIV-infected patients with MDR-TB having a lower median CD4 count (90/mm$^3$) than those without MDR-TB (120/mm$^3$). In addition, the association between RR-TB and positive HIV status may reflect the development of acquired drug resistance. This could be the consequence of "preferential adherence" to antiretroviral medications at the expense of anti-TB medications among patients co-infected with HIV and TB [39]. Our findings are supported by recent evidence. A systematic review and meta-analysis reported that HIV infection significantly increased the odds of MDR-TB, emphasizing the importance of early diagnosis, comprehensive drug susceptibility testing, and integrated TB/HIV management to reduce the burden of drug-resistant disease [44]. Similarly, a recent review highlighted that HIV-associated immune dysfunction, delayed diagnosis, and barriers to preventive therapy continue to contribute substantially to the global burden of TB, particularly in high-burden settings [35]. These findings further support our observation that HIV remains an important factor associated with MDR-TB, particularly in Europe and South America. As mentioned above, in Europe and South America, the risk of MDR-TB and DR-TB was linearly associated with alcohol use. Heavy alcohol consumption has been linked to a 35% increased risk of TB infection [4]. Alcohol consumption is associated with a higher incidence of MDR-TB and XDR-TB [45]. In recent years, some studies have indicated that alcohol use is an independent marker of MDR-TB [27]. Alcohol use can cause decreased immunity, liver damage, and nutritional deficiencies, all of which may contribute to sensitive and resistant TB infection [46]. Given the influence of alcohol use on TB drug resistance, the development of MDR-TB among people who consume alcohol in Europe and South America should be monitored.

The network analysis revealed a different pattern of MDR-TB risk in men (mMDR-TB) and women (fMDR-TB) in various regions. mMDR-TB was linearly associated with smoking (in all regions, Asia, and Africa) and HIV infection (in Europe). In contrast, fMDR-TB was associated with alcohol use (in all regions and Africa) and increased with age in Asia and Europe. In addition, using the Spearman index (nonlinear), network analysis revealed that mMDR-TB was associated with adulthood in all regions (Asia, Africa, South America, and Europe), whereas fMDR-TB was associated with rural residence, older age, and childhood in Asia, Africa, and Europe, respectively. It has been shown that there are sex-specific differences in DR [47]. Mughal *et al.* (2025) [23] found that age and gender were not significantly associated with MDR-TB. However, Daneshi *et al*. (2025) [25] found that comorbidities such as diabetes and HIV, along with male sex and older age, were significant contributing factors, particularly in XDR-TB cases. According to a worldwide analysis led by the WHO, women may be more susceptible to drug-resistant illnesses than men, which is an underappreciated aspect of the rising threat of antimicrobial resistance [48]. However, beliefs that men should be the primary earners, as well as time restrictions associated with a regular job,

might contribute to men delaying diagnosis and treatment for infections, particularly MDR-TB [49]. This might explain why mMDR-TB was associated with adulthood in our research. According to the WHO, gender influences people's exposure to diseases, what they do to prevent infections, and whether they seek prompt medical attention or try treating themselves. Unfortunately, most national action plans on DR exclude sex or gender. According to the survey, more than 70% of nations do not account for gender inequities in drug-resistant infection control strategies. By 2024, more than 170 nations had established DR national action plans, but only 27 had disaggregated key data by gender, geographic region, income, and other criteria [49]. The unavailability of data disaggregated by gender constitutes a key impediment to alleviating inequities through targeted health interventions and inclusive policy frameworks [49]. In addition, the strong association between MDR-TB and adulthood in men might be due to the fact that middle-aged men are more likely than children and women to engage in behaviors such as smoking and drinking, all of which may increase susceptibility to MDR-TB among patients with TB. The present findings indicate that the risk factors for MDR-TB may show a sex- and geographically specific distribution, which should be considered in interventions and policy frameworks.

Several limitations should be acknowledged. First, although the article mentions various potential risk factors for MDR-TB, several known risk factors for MDR-TB, including diabetes, treatment history, treatment interruption or default, close contact with an MDR-TB patient, malnutrition or low body mass index, socioeconomic status (income and education), imprisonment, homelessness, occupation as a healthcare worker, BCG vaccination, drug susceptibility testing methodology, and level of urbanization, were not included in the analysis because these factors were not consistently reported in the included studies. Future larger well-designed studies should be prospective and include other factors that may be associated with MDR-TB emergence and transmission. Second, the observational nature of the included studies limits the ability to establish causal relationships. Third, the analysis accounts for between-study variability; however, this heterogeneity, along with differences in methodology, populations, and definitions used in the primary studies, could affect the results. Therefore, these limitations should be considered when interpreting the results. Further multicenter investigations addressing the epidemiology and management of MDR-TB are needed and should focus on patient groups in which multiple risk factors may interact to produce diverse clinical presentations.

In conclusion, the multi-step study identified factors associated with MDR-TB, including HIV, smoking, alcohol consumption, and living in certain geographical locations. Because the prevalence of MDR-TB and its contributing factors are not uniform, prevention and control strategies should be region-specific rather than universal. It may be concluded from the study that different sets of measures may need to be implemented in different regions, given the disparity in the prevalence of factors associated with MDR-TB. Promoting smoking cessation and expanding the availability of treatment in Asia and Africa may be warranted, whereas HIV-TB programs and interventions targeting alcohol use are more relevant in the European and South American regions. This approach may support efficient disease monitoring and control by increasing adherence and awareness among the population in a particular region. This information may be useful for screening and early detection of MDR-TB among the identified risk groups and may help in implementing appropriate interventions to prevent the spread of the disease.

## Funding

No external funding.

## Ethical approval

Not applicable.

## Conflict of interest

The authors declare no conflict of interest.

## References

1. MacNeil AGP, Sismanidis C, Date A, Maloney S, Floyd K, Floyd K. Global epidemiology of tuberculosis and progress toward meeting global targets-worldwide, 2018. MMWR Morb Mortal Wkly Rep 2020; 69: 281-5.
2. Lange C, Chesov D, Heyckendorf J, Leung CC, Udwadia Z, Dheda K. Drug-resistant tuberculosis: an update on disease burden, diagnosis and treatment. Respirology 2018; 23: 656-73.
3. Mazurek GH. Division of tuberculosis elimination, national center for HIV, STD, and TB prevention, centers for disease control and prevention (CDC). Guidelines for using the QuantiFERON-TB gold test for detecting Mycobacterium tuberculosis infection, United States. MMWR Recomm Rep 2005; 54: 49-55.
4. World Health Organization. Global tuberculosis report 2022, https://www.who. int/teams/global- tuberculosis- programme/tb-reports; 2022.
5. Tobin EH, Tristram D. Tuberculosis Overview. In StatPearls. StatPearls Publishing (2024).
6. Buonsenso D, Autore G, Cusenza F, Passadore L, Bonanno F, Esposito S. Multidrug-resistant tuberculosis in children: are the same therapy options available worldwide? Int J Infect Dis 2023; 130 Suppl 1: S16-9.
7. World Health Organization. Global Tuberculosis Report 2020. Geneva: World Health Organization, Licence: CC BY-NC-SA 30 IGO; 2020.

8. Murray JF. A century of tuberculosis. Am J Respir Crit Care Med 2004; 169: 1181-6.
9. Eddabra R, Neffa M. Mutations associated with rifampicin resistance in Mycobacterium tuberculosis Isolates from Moroccan patients: systematic review. Interdiscip Perspect Infect Dis 2020; 2020: 5185896.
10. Unissa AN, Subbian S, Hanna LE, Selvakumar N. Overview on mechanisms of isoniazid action and resistance in Mycobacterium tuberculosis. Infect Genet Evol 2016; 45: 474-92.
11. Zhou A, Nawaz M, Duan Y, et al. Molecular characterization of isoniazid-resistant Mycobacterium tuberculosis isolates from Xi'an, China. Microb Drug Resist 2011; 17: 275-81.
12. Luo D, Chen Q, Xiong G, et al. Prevalence and molecular characterization of multidrug-resistant M. tuberculosis in Jiangxi province, China. Sci Rep 2019; 9: 7315.
13. Chen Y, Zhao B, Liu HC, et al. Prevalence of mutations conferring resistance among multi- and extensively drug-resistant Mycobacterium tuberculosis isolates in China. J Antibiot 2016; 69: 149-52.
14. Wan L, Guo Q, Wei JH, et al. Accuracy of a reverse dot blot hybridization assay for simultaneous detection of the resistance of four anti-tuberculosis drugs in Mycobacterium tuberculosis isolated from China. Infect Dis Poverty 2020; 9: 38.
15. Ahmad N, Javaid A, Sulaiman SA, Ming LC, Ahmad I, Khan AH. Resistance patterns, prevalence, and predictors of fluoroquinolones resistance in multidrug resistant tuberculosis patients. Braz J Infect Dis 2016; 20: 41-7.
16. Mohammed KAS, Khudhair GS, Al-Rabeai DB. Prevalence and drug resistance pattern of Mycobacterium tuberculosis isolated from tuberculosis patients in Basra, Iraq. Pol J Microbiol 2022; 71: 205-15.
17. Urassa W, Mugusi F, Villamor E, et al. Primary antimicrobial resistance among Mycobacterium tuberculosis isolates from HIV seropositive and HIV seronegative patients in Dar es Salaam Tanzania. BMC Res Notes 2008; 1: 58.
18. Abdella K, Abdissa K, Kebede W, Abebe G. Drug resistance patterns of Mycobacterium tuberculosis complex and associated factors among retreatment cases around Jimma, Southwest Ethiopia. BMC Public Health 2015; 15: 599.
19. Ichsan I, Redwood-Campbell L, Mahmud NN, et al. Risk factors of MDR-TB and impacts of COVID-19 pandemic on escalating of MDR-TB incidence in lower-middle-income countries: a scoping review. Narra J 2023; 3: e220.
20. Kowsar R, Komeili M, Sadeghi N, Sadeghi K. Multistep analysis reveals the relationship between blood indices at the time of ovum pick-up and in vitro embryo production in heifers. Theriogenology 2021; 159: 153-64.
21. Kowsar R, Mansouri A, Sadeghi N, et al. A multilevel analysis identifies the different relationships between amino acids and the competence of oocytes matured individually or in groups. Sci Rep 2020; 10: 16082.
22. Alemu A, Bitew ZW, Diriba G, Gumi B. Risk factors associated with drug-resistant tuberculosis in Ethiopia: a systematic review and meta-analysis. Transbound Emerg Dis 2022; 69: 2559-72.
23. Mughal MA, Imran A, Khan HU, et al. Prevalence of multidrug-resistant tuberculosis and its association with previous treatment history in adults. Cureus 2025; 17: e88204.
24. Diriba G, Alemu A, Yenew B, et al. Epidemiology of extensively drug-resistant tuberculosis among patients with multidrug-resistant tuberculosis: a systematic review and meta-analysis. Int J Infect Dis 2023; 132: 50-63.
25. Daneshi S, Mehni EB, Kamali M, et al. Prevalence and contributing factors of drug-resistant tuberculosis (DR-TB) in Iran: a systematic review. BMC Infect Dis 2025; 25: 1004.
26. Salari N, Kanjoori AH, Hosseinian-Far A, Hasheminezhad R, Mansouri K, Mohammadi M. Global prevalence of drug-resistant tuberculosis: a systematic review and meta-analysis. Infect Dis Poverty 2023; 12: 57.
27. Song WM, Li SJ, Liu JY, et al. Impact of alcohol drinking and tobacco smoking on the drug-resistance of newly diagnosed tuberculosis: a retrospective cohort study in Shandong, China, during 2004-2020. BMJ Open 2022; 12: e059149.
28. Ali MH, Al-Rasheedy AA, Hassali MA, Dan Kibuule D, Godman B. Predictors of multidrug-resistant tuberculosis (MDR-TB) in Sudan. Antibiotics 2019; 8: 90.
29. Amere GA, Nayak P, Salindri AD, Narayan KMV, Magee MJ. Contribution of smoking to tuberculosis incidence and mortality in high-tuberculosis-burden countries. Am J Epidemiol 2018; 187: 1846-55.
30. Silva DR, Munoz-Torrico M, Duarte R, et al. Risk factors for tuberculosis: diabetes, smoking, alcohol use, and the use of other drugs. J Bras Pneumol 2018; 44: 145-52.
31. Wang MG, Huang WW, Wang Y, et al. Association between tobacco smoking and drug-resistant tuberculosis. Infect Drug Resist 2018; 11: 873-87.
32. Vidyasagaran AL, Readshaw A, Boeckmann M, et al. Is tobacco use associated with risk of recurrence and mortality among people with TB? A systematic review and meta-analysis. Chest 2024; 165: 22-47.
33. Chung C, Lee KN, Han K, Shin DW, Lee SW. The effect of smoking on nontuberculous mycobacterial pulmonary disease and tuberculosis: a nationwide retrospective cohort study. Sci Rep 2024; 14: 22653.
34. Zhao Y, Xu S, Wang L, et al. National survey of drug-resistant tuberculosis in China. N Engl J Med 2012; 366: 2161-70.
35. Meintjes G, Maartens G. HIV-associated tuberculosis. N Engl J Med 2024; 391: 343-55.
36. Duffey M, Shafer RW, Timm J, et al. Combating antimicrobial resistance in malaria, HIV and tuberculosis. Nat Rev Drug Discov 2024; 23: 461-79.
37. Eldholm V, Rieux A, Monteserin J, et al. Impact of HIV co-infection on the evolution and transmission of multidrug-resistant tuberculosis. Elife 2016; 5: e16644.
38. Frieden TR, Sterling T, Pablos-Mendez A, Kilburn JO, Cauthen GM, Dooley SW. The emergence of drug-resistant tuberculosis in New York City. N Engl J Med 1993; 328: 521-6.
39. Amrita D, Nesri P, O'Donnellb CM. Preferential adherence to antiretroviral therapy over tuberculosis (TB) treatment: a qualitative study of drug–resistant TB/HIV co-infected patients in South Africa. Glob Public Health 2014; 9: 1107-16.
40. Ismail NA, Mvusi L, Nanoo A, et al. Prevalence of drug-resistant tuberculosis and imputed burden in South Africa: a national and sub-national cross-sectional survey. Lancet Infect Dis 2018; 18: 779-87.
41. Timire C, Metcalfe JZ, Chirenda J, et al. Prevalence of drug-resistant tuberculosis in Zimbabwe: a health facility-based cross-sectional survey. Int J Infect Dis 2019; 87: 119-25.
42. Hannan MM, Peres H, Maltez F, et al. Investigation and control of a large outbreak of multidrug-resistant tuber-

culosis at a central Lisbon hospital. J Hosp Infect 2001; 47: 91-7.
43. Saldanha N, Runwal K, Ghanekar C, Gaikwad S, Sane S, Pujari S. High prevalence of multi drug resistant tuberculosis in people living with HIV in Western India. BMC Infect Dis 2019; 19: 391.
44. Song Y, Jin Q, Qiu J, Ye D. A systematic review and meta-analysis on the correlation between HIV infection and multidrug-resistance tuberculosis. Heliyon 2023; 9: e21956.
45. Miller AC, Gelmanova IY, Keshavjee S, et al. Alcohol use and the management of multidrug-resistant tuberculosis in Tomsk, Russian Federation. Int J Tuberc Lung Dis 2012; 16: 891-6.
46. Zhao LL, Huang MX, Xiao TY, et al. Prevalence, risk and genetic characteristics of drug-resistant tuberculosis in a tertiary care tuberculosis hospital in China. Infect Drug Resist 2019; 12: 2457-65.
47. McQuaid CF, Horton KC, Dean AS, Knight GM, White RG. The risk of multidrug- or rifampicin-resistance in males versus females with tuberculosis. Eur Respir J 2020; 56: 2000626.
48. Wong C. Drug-resistant infections more likely to strike women, says WHO. Nature 2024. doi: 10.1038/d41586-024-01476-9.
49. WHO guidance on gender inequalities and antimicrobial resistance. Release 16 September 2024. https://www.who.int/news/item/16-09-2024-who-releases-guidance-on-gender-inequalities-and-antimicrobial-resistance.